The Graft Imaging to Improve Patency (GRIIP) clinical trial results

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Objective: This trial aimed to determine whether intraoperative graft assessment with criteria for graft revision would decrease the proportion of patients with 1 or more graft occlusions or stenoses or major adverse cardiac events 1 year after coronary artery bypass grafting.

Methods: A single-center, randomized, single-blinded, controlled clinical trial was designed. Patients were randomized to either of 2 groups: intraoperative graft patency assessment using indocyanine-green fluorescent angiography and transit-time flowmetry, with graft revision according to a priori criteria (imaging group), or standard intraoperative management (control group). Patients underwent follow-up angiography at 1 year.

Results: Between September 2005 and August 2008, 156 patients undergoing isolated coronary bypass grafting were enrolled (imaging, n = 78; control, n = 78). Demographic and angiographic characteristics were similar between groups. Operative, crossclamp, and cardiopulmonary bypass times were all nonsignificantly longer in the imaging arm. The number of grafts per patients was similar (imaging, 3.0 ± 0.7; control, 3.0 ± 0.7). The frequency of major adverse cardiac events (death, myocardial infarction, repeat revascularization) was not different between groups at 1 year postoperatively (imaging, 7.7%; control, 7.7%). One-year angiography was performed in 107 patients (imaging, 55 patients/160 grafts; control, 52 patients/152 grafts). The proportion of patients with 1 graft occlusion or more was comparable in the imaging (30.9%) and control (28.9%) groups (relative risk [95% confidence interval], 1.1 [0.6–1.9]; $P = .82$), as were other graft patency end points. The incidence of saphenous vein graft occlusion was high in both groups.

Conclusions: Routine intraoperative graft assessment is safe but does not lead to a marked reduction in graft occlusion 1-year after bypass grafting. The incidence of saphenous vein graft failure remains high despite contemporary practice and routine intraoperative graft surveillance. (J Thorac Cardiovasc Surg 2010;139:294-301)

Supplemental material is available online.

The success of coronary artery bypass graft (CABG) surgery is contingent on using durable conduits to construct quality anastomoses onto appropriate target coronary vessels. Medical therapies, such as postoperative aspirin and statin administration, and increased use of arterial grafting have significantly improved graft patency.[1-4]

Despite the highly favorable outcomes of CABG, a significant number of patients experience early graft failure. Historical and contemporary angiographic studies have demonstrated up to 15% of saphenous vein grafts and 8% of left internal thoracic artery grafts are occluded 1 week after CABG.[2,5-8] One postulate is that this is predominantly a result of surgical/technical problems that may be repairable at the time of the operation, if identified. Poor graft patency has been clearly correlated with markedly increased 30-day and late mortality.[9]

Tools for intraoperative patency assessment are widely described in the literature. Indocyanine green (ICG) fluoroscopy and transit-time ultrasound flowmetry (TTF) are validated and easy-to-use means of identifying graft errors intraoperatively.[10-14] However, they pose potential risks to the patient by prolonging crossclamp and cardiopulmonary bypass (CPB) times, and they theoretically could lead to poorer anastomosis quality and patency by inappropriate revision.

The primary objective of this study was to assess whether a strategy of intraoperative patency assessment and graft revision can decrease the rate of graft occlusions, significant stenosis, and/or major adverse clinical events (MACE) at 1 year after CABG. This is the first contemporary, randomized, controlled clinical trial to answer this question, which

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ClinicalTrials.gov Identifier NCT00187421.
Disclosures: None.
Read at the Eighty-ninth Annual Meeting of The American Association for Thoracic Surgery (C. Walton Lillehei Resident Forum), Boston, Massachusetts, May 9–13, 2009.
Received for publication May 8, 2009; revisions received Sept 8, 2009; accepted for publication Sept 28, 2009; available ahead of print Dec 14, 2009.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.09.048

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CPB = cardiopulmonary bypass
GRIIP trial = Graft Imaging to Improve Patency trial
ICG = indocyanine green
MACE = major adverse clinical event
TTF = transit-time ultrasound flowmetry

is of undeniable relevance to improving outcomes and applying quality assurance to the contemporary and future practice of CABG surgery.

METHODS

The study was approved by the institutional research ethics board and informed patient consent was acquired. The study design was a single-center, randomized, single-blinded, controlled clinical trial (ClinicalTrials.gov Identifier NCT00187421).

Patient Population

Eligibility criteria included the following: age older than 18 years; elective or emergency isolated, primary CABG with or without CPB; and left ventricular ejection fraction greater than 20%. Exclusion criteria included the following: those with contraindications to receiving intraoperative ICG dye (iodine allergy, severe liver disease affecting ICG excretion), contraindications to follow-up angiography (chronic renal failure [creatinine > 180 μmol/L], severe peripheral vascular disease, coagulopathy, or obligatory use of anticoagulants), or geographically inaccessible to follow-up.

Study Design and Randomization

Patients were randomized to a control or experimental (imaging) group in a 1:1 allocation ratio. Control patients had intraoperative assessment of graft patency based on clinical judgment of the attending surgeon using criteria including probe patency, the ease of graft injection after completion of the distal anastomosis, appearance and palpation of the completed graft, the electrocardiogram, wall motion according to transesophageal echocardiography, and hemodynamic stability. The experimental group had intraoperative graft assessment using fluorescence angiography (Novadaq SPY ICG angiography system; Novadaq Technologies, Toronto, Ontario, Canada) and TTF (Medtronic MediStim flowmeter, Medtronic, Inc, Newport, Calif), with a strategy of graft revision based on a priori criteria, in addition to clinical judgment.

A priori criteria for graft revision in the imaging group were any one of the following ICG fluoroscopy findings: (1) occluded graft (no distal vessel opacification seen), (2) greater than 50% stenosis by visual assessment of either the graft body or the proximal or distal anastomosis site, or (3) a stenosis of more than 50% in the native vessel within the first 1 cm distal to the anastomosis. Grafts were also required to be revised if two of the following three TTF findings were found at intraoperative graft assessment: (1) a pulsatility index (resistance) greater than 5, (2) a diastolic flow fraction less than 50%, and/or (3) mean flow less than 10 mL/min. If either ICG or TTF criteria were met, grafts had to be revised.

Randomization was revealed after the sternotomy was performed and the operative strategy finalized, namely, the choice of bypass conduits and the use of CPB (on-pump vs off-pump). Randomization was via sealed envelope allocation in blocks of 4 to 6. Crossovers were allowed; final analysis was performed on an intent-to-treat basis.

Study Procedures and Follow-up

Intraoperatively, in both groups, distal anastomoses were allowed to be instrumented using probes or intracoronary shunts as per surgeon routine. Intraoperative ICG angiography was performed with the Novadaq SPY system as per a defined protocol, by experienced users.[10,11] For on-pump cases, our technique was to hand inject free grafts after the distal anastomosis was constructed, perform CPB pump (arterial line) injections for in situ internal thoracic artery fluoroscopic assessment, and inject into the central venous line for proximal anastomosis assessment, after separation from CPB. For off-pump cases, we performed hand injections of the distal anastomoses of free grafts and injection into the central venous line for in situ grafts and proximal anastomoses.

TTF was performed with the MediStim TTF system.[12-14] In on-pump cases, TTF measurements were performed after patients had been weaned from CPB and achieved stable heart rhythm and hemodynamics. Appropriate sized probes (2–4 mm) were used and measurements deemed appropriate once adequate (>50%) contact was determined by the acoustic coupling indicator.

Postoperative management was standardized for both groups. All patients received aspirin (or other antiplatelet therapy if aspirin intolerant) within 6 hours postoperatively. All other medications were prescribed as clinically indicated, including the use of statins, beta-blockers, calcium-channel blockers for patients receiving radial artery grafts, and angiotensin-converting enzyme inhibitors.

Patients had routine clinical assessments before discharge and at 3 months, 6 months, and 12 months after the operation. These included routine serial electrocardiograms, blood work, a clinical examination, and enquiries into any symptoms, hospitalizations, investigations, and medication use.

Patients underwent angiography at approximately 1 year, either by conventional radiography or 64-slice computed tomographic angiography (which has been validated at our institution). Initially, the trial protocol required conventional x-ray angiography at 4 to 12 weeks after CABG. However, this was amended to include either x-ray angiography or less invasive computed tomographic angiography, up to 1 year after CABG, to improve patient compliance with follow-up angiography.

End Points

The primary end point compared the imaging group to the control group with respect to the proportion of patients with 1 or more totally (100%) occluded grafts at 1 year's follow-up angiography. Secondary end points compared the 2 groups regarding the proportion of patients with 1 or more graft with a significant (50%–99%) stenosis, the proportion of patients with graft occlusion or significant stenosis, as well as the incidence of perioperative clinical events and MACE (death, myocardial infarction, repeat revascularization, or percutaneous coronary intervention) at 30 days and 1 year. Grafts with diffuse narrowing (to <1 mm) were recorded as ''string signs.'' Postoperative angiograms, serial electrocardiograms, and clinical information were reviewed by a blinded Angiographic and Clinical Endpoints Committee. Perioperative myocardial infarction was defined as the presence of new or deeper Q waves on 2 or more contiguous leads on the postoperative 12-lead electrocardiogram or a peak creatine kinase MB greater than 70 μg/mL.[15]

Statistical Analysis

Continuous variables were reported as mean $\pm$ standard deviation and categorical variables as a frequency and proportion. All analyses were performed on an intention-to-treat basis. The primary (ie, graft occlusion) and secondary end points (ie, >50% stenosis and >50% stenosis or occlusion) were evaluated on a patient level and were expressed with relative risks and 95% confidence intervals. Graft patency was also recorded per distal anastomosis as an ancillary outcome. Statistical differences between groups were determined by the χ^2 test and Fisher's exact test when appropriate and with a Wilcoxon rank sum test for differences in lengths of follow-up. SAS version 9.1 (SAS, Inc, Cary, NC) was use to execute statistical

TABLE 1. Preoperative patient demographic and angiographic characteristics, by group (N = 156)

	Imaging group		Control group	
	All patients (n = 78)	Patients with angiography (n = 55)	All patients (n = 78)	Patients with angiography (n = 52)
Age, y ± SD	62.3 ± 12.3	60.7 ± 9.5	64.3 ± 8.9	63.9 ± 9.0
Female, n (%)	9 (11.5)	5 (9.1)	10 (12.8)	5 (9.6)
Diabetes, n (%)	24 (30.8)	13 (23.6)	25 (32.1)	16 (30.8)
Hypertension, n (%)	53 (67.9)	38 (69.1)	61 (78.2)	39 (75.0)
Hyperlipidemia, n (%)	69 (88.5)	52 (94.5)	73 (93.6)	44 (84.6)
Smoking history, n (%)	39 (50.0)	26 (47.3)	43 (55.1)	28 (53.8)
Family history, n (%)	32 (41.0%)	27 (49.1)	21 (26.9)	17 (32.7)
Previous MI, n (%)	28 (35.9)	21 (38.2)	27 (34.6)	16 (30.8)
LVEF < 35%, n (%)	8 (10.3)	4 (7.3)	5 (6.4)	3 (5.8)
CCS class ≥ III, n (%)	32 (41.0)	21 (38.2)	31 (39.7)	18 (34.6)
Preoperative creatinine (μmol/L) ± SD	90.0 ± 21.5	86.8 ± 17.6	87.1 ± 17.2	88.4 ± 18.5
Peripheral vascular disease, n (%)	6 (7.7)	4 (7.3)	5 (6.4)	2 (3.8)
Previous PCI, n (%)	9 (11.5)	8 (14.5)	9 (11.5)	5 (9.6)
Nonelective surgery, n (%)	12 (15.4)	9 (16.4)	15 (19.2)	8 (15.4)
Left main disease, n (%)	10 (12.8)	4 (7.3)	15 (19.2%)	11 (21.2)
No. of diseased vessels, 1/2/3, n (%)	6/25/47 (7.7/32.1/60.3)	6/15/34 (10.9/27.3/61.8)	4/21/53 (5.1/26.9/67.9)	2/16/34 (3.8/30.8/65.4)

SD, Standard deviation; *MI,* myocardial infarction; *LVEF,* left ventricular ejection fraction; *CCS,* Canadian Cardiovascular Society; *PCI,* percutaneous coronary intervention.

tests. All authors had full access to and take full responsibility for the integrity of the data. All of us have read and agreed to the manuscript as written.

RESULTS

Between September 2005 and August 2008, 156 patients were enrolled into the Graft Imaging to Improve Patency (GRIIP) trial: 78 were randomized to the imaging group and 78 to the control group. Balance from randomization is shown in Table 1.

Table 2 summarizes the operative characteristics of the imaging versus control patients. The total number of grafts constructed and grafts per patient were no different between groups. Operative times (total, CPB, and crossclamp) were longer in the imaging group; however, this difference was not statistically significant.

Table 2 displays the adherence to the protocol in both the imaging and control groups. There were 3 crossovers in the control arm (3.4%), involving 8 grafts, which were assessed using the experimental intervention (ICG and/or TTF) on the basis of surgeon suspicion regarding graft anastomosis quality. None of these 8 grafts met the a priori criteria for graft revision, yet 5 grafts were revised as per surgeon decision. Conversely, in the imaging group, 8 (3.6%) of the total 234 grafts constructed met criteria for revision; however, only 4 (1.7%) grafts (involving 4 different patients) were revised (3 of which were from the 8 meeting revision criteria and another 1 that was revised on the basis of surgeon preference [ICG and TTF were normal]). The unrevised 4 grafts (protocol violations) were attributed to the surgeon's judgment that revision was unwarranted and unlikely to result in a better outcome. A small proportion of patients in the imaging group received no intraoperative assessment (7 grafts, 3.0%, in 3 patients). This nonadherence to the protocol was due to technical malfunctions related to imaging and transit-time systems.

Angiography End Points

Follow-up angiographic results are shown in Table 3. A total of 107 patients received follow-up angiographic assessment (x-ray angiography, 23; computed tomographic angiography, 84). These comprised 55 patients in the imaging group and similarly 52 patients in the control group, at a mean follow-up of 12.1 ± 10.5 months and 13.3 ± 9.8 months after CABG, respectively ($P = .51$). The preoperative characteristics of the entire group and the patients who underwent angiography were similar (Table 1). In addition, there were no differences between the imaging and control patients who completed follow-up angiography. The reasons precluding follow-up angiography were as follows: death in 1 patient, late refusal in 30 patients, new contraindications to research angiography in 14 patients, and lost to follow-up in 4 (all of whom had moved out the country).

Overall, 13.8% of all studied grafts (43/312) were occluded. The primary study outcome, the proportion of patients with 1 or more graft occlusions at 1 year after

TABLE 2. Operative characteristic and intraoperative graft assessment details using indocyanine-green fluoroscopy (ICG) and transit-time flowmetry (TTF), by group (N = 156)

	Imaging group (n = 78)	Control group (n = 78)
Operative characteristics		
Total No. of bypass grafts	234	233
No. of bypass grafts/ patient, mean ± SD	3.0 ± 0.7	3.0 ± 0.7
Number of arterial grafts/ patient, mean ± SD	1.4 ± 0.6	1.4 ± 0.5
LITA/RITA/RA grafts, n (% of patients)	74/7/29 (94.8/9.0/37.2)	78/6/22 (100/7.7/28.2)
Off-pump, n (%)	7 (9.0)	5 (6.4)
Crossclamp time, min, mean ± SD	109 ± 32	97 ± 22
CPB time, min, mean ± SD	128 ± 37	116 ± 25
Total operating room time, min, mean ± SD	336 ± 76	319 ± 83
Intraoperative graft assessment details		
Grafts assessed with both ICG and TTF, n (%)	170 (72.6)	6 (2.6)
Grafts only assessed with ICG, n (%)	53 (22.6)	2 (0.9)
Grafts only assessed with TTF, n (%)	4 (1.7)	0 (0)
Grafts not assessed with ICG or TTF, n (%)	7 (3.0)	225 (96.6)
Grafts meeting revision criteria, n (%)	8/234 (3.6)	0/8 (0)
Revised grafts, n (%)	4 (1.7)	5 (2.1)

SD, Standard deviation; *LITA*, left internal thoracic artery; *RITA*, right internal thoracic artery; *RA*, radial artery; *CPB*, cardiopulmonary bypass.

CABG, was similar in the 2 arms (imaging, 30.9%; control, 28.9%, relative risk [95% confidence intervals], 1.1 [0.6–1.9]; $P = .82$). Nor was any difference noted in our secondary angiographic outcomes of 1 or more significant stenoses (50%–99%), or any occlusion or significant stenosis, between the 2 groups. Table 3 also demonstrated that the rate of occlusion or stenosis was substantially higher in saphenous vein grafts (49/159, 30.8%) than in arterial grafts (6/153, 3.9%).

At approximately the 1-year angiographic assessment, there were no occlusions of the left internal thoracic arteries in the imaging group and 2 occlusions in the control group ($P = .22$); there were no right internal thoracic arteries occluded in either group. Six string signs were noted on 1-year angiography in 6 patients in the imaging arm compared with 2 string signs at follow-up angiography in the control arm (both in the same patient). Stratified analysis looking at time to follow-up angiography did not reveal any differences in outcomes between the 2 groups.

Excluding grafts with criteria for revision (see subsequent paragraph), intraoperative ICG angiography indicated that all grafts assessed that were occluded on subsequent follow-up angiography were patent intraoperatively. TTF also did not distinguish between grafts that subsequently became occluded and those that remained patent according to mean flow (30.5 ± 13.4 vs 33.9 ± 22.7 mL/min), pulsatility index (3.09 ± 1.87 vs 3.12 ± 3.11), or diastolic fraction (61.2% ± 13.3% vs 65.5% ± 12.6 %).

Grafts Revised or Meeting Revision Criteria

Eight grafts in the imaging group met revision criteria according to intraoperative ICG and/or TTF assessments. In all these grafts, ICG fluorescence angiography showed normal findings, but revision criteria were met for TTF measures. Of the 8 total grafts that received intraoperative assessment measures and met criteria for revision (1 left internal thoracic artery, 1 radial artery, 6 saphenous vein grafts), 3 were revised (1 radial artery, 2 saphenous vein grafts). Six of these 8 grafts were studied postoperatively; 1 of 2 revised grafts was occluded whereas 3 of 4 nonrevised grafts were patent.

Six grafts were either not imaged or did not meet revision criteria but were revised on the basis of clinical criteria alone (4 left internal thoracic artery grafts, 2 saphenous vein grafts). Five of these 6 grafts were assessed postoperatively; 2 grafts (2 left internal thoracic arteries) were occluded (see Appendix E1 online)

Perioperative Outcomes and MACE

There were no differences in the incidence of perioperative events or MACE at 1 year between the 2 groups (Table 4). Concomitant medical management was similar in the imaging and control patients at discharge and at 1 year after surgery (Table 5).

DISCUSSION

The GRIIP trial aimed to determine whether intraoperative graft assessment with graft revision criteria would result in improved angiographic patency and clinical outcomes at 1 year after CABG surgery when compared with routine intraoperative assessment without imaging or flow measurement tools. The study demonstrated that routine intraoperative graft assessment was safe and feasible but did not lead to a significant reduction in the frequency of 1 or more graft occlusions, stenoses, or MACEs at 1 year after CABG.

The GRIIP trial also showed that the incidence of 1-year saphenous vein graft occlusion remains high, despite the coexistent use of evidence-based care including antiplatelets and statins in a very high proportion of patients. This observation is consistent with other contemporary studies, including the PREVENT IV trial,[3] a multicenter randomized trial that enrolled 3014 patients after CABG between 2002 and 2003. The authors found 45% of all patients had 1 or more saphenous vein graft occlusions. In fact, 25% of all

TABLE 3. Angiographic patency results at 1 year, by group

	Imaging group (n = 55)	Control group (n = 52)	RR (95% CI)	*P* value
Primary end point				
Total No. of grafts	160	152		
Graft occlusions, n (%)	24/160 (15.0)	19/152 (12.5)	1.2 (0.7–2.1)	.52
Saphenous vein grafts	24/79 (30.4)	17/80 (21.3)		
Arterial grafts	0/81 (0)	2/72 (2.8)		
Patients with ±1 graft occlusion	**17 (30.9)**	**15 (28.9)**	**1.1 (0.6–1.9)**	**.82**
Secondary end points				
Grafts with >50% stenosis, n (%)	4/160 (2.5)	8/152 (5.3)	0.5 (0.1–1.5)	.20
Saphenous vein grafts	1/79 (1.3)	7/80 (8.8)		
Arterial grafts	3/81 (3.7)	1/72 (1.4)		
Patients with ≥1 graft with >50% stenosis	**3 (5.5)**	**8 (15.4)**	**0.4 (0.1–1.3)**	**.09**
Grafts with a >50% stenosis or occlusion, n (%)	28/160 (17.5)	27/152 (17.8)	1.0 (0.6–1.6)	.95
Saphenous vein grafts	25/79 (31.7)	24/80 (30.0)		
Arterial grafts	3/81 (3.7)	3/72 (4.2)		
Patients with ≥1 graft with >50% stenosis or occlusion	**19 (34.6)**	**22 (42.3)**	**0.8 (0.5–1.3)**	**.41**

Bold face indicates primary and secondary angiographic end points. *RR,* Relative risk; *CI,* confidence interval.

saphenous vein grafts were occluded at 1-year angiography, similar to our study findings.

It is our contention that saphenous vein graft patency is likely worse in the current era than that seen previously related to the competing revascularization strategy of percutaneous coronary intervention. Percutaneous coronary intervention has expanded its clinical indications. As a result, patients referred for surgery have more diffuse, distal, small vessels (<2 mm) and often calcific disease and/or stent failure. In a previous meta-analysis of antithrombotic graft patency trials, 588 (13.4%) of 4400 saphenous vein grafts had occluded at the distal anastomosis in the actively treated patients.[16] Almost all of these studies had been completed in the 1980s. The multicenter Radial Artery Patency Study[17] compared the patency of the radial artery to the saphenous vein graft in patients who served as their own controls, recruited from 1996 through 2001. The results showed 8% of radial artery bypass conduits and 13% of saphenous vein graft conduits were occluded at 1-year angiography. Concerns have been raised that saphenous vein graft occlusion may be increased when veins are harvested by a minimally invasive technique[18] or by skeletonized saphenous vein graft harvesting, by increasing trauma and endothelial dysfunction. In this trial, saphenous vein grafts were harvested under direct vision by an open technique. Future innovations, pharmacologic or technical (eg, no-touch vein harvesting),[19] addressing improvement in saphenous vein graft patency should be pursued.

Along with venous conduit predilection for failure, the GRIIP trial results also indicate that 1-year graft failure was likely related to fibrointimal hyperplasia as opposed to early technical errors. In the group of patients who received imaging, it was found that only 8 (3.6%) of a total of 225 grafts constructed had intraoperative flow assessment data that met revision criteria in the operating room. Even if all these grafts were related to technical error, this estimate is low in comparison with previous literature reporting early (intraoperative or < 1 week after CABG) technical graft failure up to 15%.[1,6] Furthermore, the imaging modalities were not sensitive considering the number of occluded or significantly stenosed grafts (28/160, 17.5%) seen at 1 year in the imaging group. Nonetheless, despite poor patency, MACE at 30 days and 1 year were low in each group, which is consistent with other large, contemporary coronary trials.[3,17]

Intraoperative graft assessment with ICG fluorescence angiography has been validated with gold-standard x-ray

TABLE 4. Postoperative clinical outcomes and MACE, by group (N = 156)

	Imaging group (n = 78)	Control group (n = 78)
In-hospital outcomes		
IABP, n (%)	1 (1.3)	0 (0)
Stroke, n (%)	0 (0)	1 (1.3)
CK-MB, mean (ng/mL) ± SD	31.9 ± 17.7	31.0 ± 34.3
Chest reopening for bleeding, n (%)	1 (1.3)	1 (1.3)
Postoperative length of stay, mean (d) ± SD	8.5 ± 7.5	7.6 ± 4.4
MACE (1 y)		
Death, n (%)	0 (0)	1 (1.3)
MI, n (%)	4 (5.1)	3 (3.8)
Repeat CABG, n (%)	0 (0)	1 (1.3)
Postoperative PCI, n (%)	2 (2.6)	1 (1.3)
Any MACE, n (%)	6 (7.7)	6 (7.7)

MACE, Major adverse clinical events; *IABP,* intra-aortic balloon pump; *CK-MB,* creatinine kinase MB fraction; *SD,* standard deviation; *MI,* myocardial infarction; *CABG,* coronary artery bypass graft surgery; *PCI,* percutaneous coronary intervention.

TABLE 5. Medications at discharge and 1 year postoperatively, by group

	Medications at discharge		Medications at 1 year	
	Imaging group (n = 78)	Control group (n = 77)	Imaging group (n = 78)	Control group (n = 78)
ACE inhibitors, n (%)	8 (10.3)	9 (11.7)	33 (42.3)	30 (39.0)
Calcium-channel blockers, n (%)	13 (16.7)	22 (28.6)	9 (11.5)	19 (24.7)
Beta-blockers, n (%)	59 (75.6)	65 (84.4)	49 (62.8)	56 (72.7)
ASA, n (%)	70 (89.7)	67 (87.0)	70 (89.7)	63 (81.8)
Anticoagulants, n (%)	8 (10.3)	7 (9.1)	4 (5.1)	5 (6.5)
Clopidogrel, n (%)	11 (14.1)	14 (18.2)	8 (10.3)	7 (9.1)
Lipid-lowering agents, n (%)	74 (94.9)	70 (90.9)	74 (94.9)	70 (90.9)
Diuretic, n (%)	4 (5.1)	1 (1.3)	10 (12.8)	9 (11.7)
Digoxin, n (%)	1 (1.3)	2 (2.6)	1 (1.3)	2 (2.6)
Amiodarone, n (%)	4 (5.1)	6 (7.8)	0 (0)	2 (2.6)

ACE, Angiotensin-converting enzyme; *ASA,* aspirin.

angiography and provides a safe, nonradiation means of angiographically depicting graft and native vessel disease intraoperatively. It is easy to use, safe, and the GRIIP trial demonstrated that it did not significantly affect operative, CPB, or crossclamp times. This is consistent with the literature to date, which also shows ICG angiography to have excellent inter-rater reliability for prompting graft revision by identifying poor patency.[10] A previous review at our center looked at TTF, ICG, and x-ray angiography as the gold standard performed within 1 week postoperatively for 139 bypass grafts.[11] The sensitivity and specificity for ICG to detect greater than 50% and 100% occlusions were 83% and 100%, respectively. For TTF these were 24% and 98% for greater than 50% and 100% occlusions, respectively. Balacumaraswami and associates[20] concluded that the combination of the emerging ICG modality to the widely available TTF resulted in improved confirmation of graft patency and reduced inappropriate revisions, when compared to TTF alone, when reviewing 266 grafts (in 100 patients) undergoing CABG.

However, the role of intraoperative angiography is clearly influenced by surgeon input. In the GRIIP trial, of the 8 (3.6%) grafts in the imaging group meeting revision criteria, half were not revised owing to surgeon concern for greater technical challenge and poorer anastomosis result with revision (protocol violations). Conversely, in the control (no imaging) group, 5 grafts were revised on the basis of surgeon discretion. It is also instructive that 4 of the 7 revised grafts with angiographic follow-up were patent, compared with 3 of 4 grafts that met revision criteria but were not revised. It appears that the results of intraoperative imaging should not be used in isolation of clinical judgment.

We designed the study to look for large treatment effects, inasmuch as we did not expect that the imaging strategy would be widely adopted by surgeons if only small differences emerged. We had fairly broad inclusion/exclusion criteria—conceivably the results may have differed if we had restricted the study to higher risk patients. Furthermore, the majority of patients underwent on-pump rather than off-pump CABG surgery. Intraoperative patency assessment is likely of greater necessity in off-pump CABG. We defined the primary and secondary patency outcomes to be reported on a per-patient basis, inasmuch as this is inherently more conservative, and we believe is clinically more relevant than reporting patency on a per–distal anastomosis basis. No benefit was observed for the primary outcome; there was a small, nonsignificant improvement in the imaging group for the secondary end point occlusion or stenosis, but this was not evident when distal anastomotic patency was analyzed separately.

In conclusion, the GRIIP trial demonstrated that routine intraoperative graft assessment with criteria for graft revision is safe and feasible. However, graft patency and clinical outcomes at 1 year were not different when compared with those in patients who did not receive intraoperative patency assessment tools. Our trial suggests that intraoperative graft patency assessment need not be used routinely, but only when clinical suspicion of graft failure exists. The other principal finding of our trial is that saphenous vein graft occlusion remains an unresolved issue in the contemporary practice of cardiac surgery.

We appreciate the efforts of Tony Chan, Nicholas Fountas, Jennifer Ku, Michael Knightingale, and Davida Petroff, who assisted in the database queries, chart reviews, and manuscript preparation.

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Discussion

Dr Munir Boodhwani *(Brussels, Belgium).* Can you comment on your power and sample size calculations? It is a smallish study with negative results. What were your assumptions?

Dr Singh. In our original protocol and proposal for funding, we hypothesized and calculated that roughly 200 patients would be required per arm. This would achieve a power of 80%, given an assumed event rate in the control group of 9% of grafts occluded, with a relative risk reduction of 60%. Although we did not actually recruit our intended sample, the event rate, occlusions in the control group, was significantly higher at 30%. As well, the relative risk reduction confidence interval included that which we had hypothesized. On the basis of these parameters, it is reasonable to assume a reasonable power and to make a meaningful conclusion from this study.

Dr Boodhwani. Was the harvesting technique for the saphenous vein similar in both groups?

Dr Singh. The method was standardized in both groups; it was the conventional, open, nonminimally invasive harvesting technique.

Dr Jennifer Sue Lawton *(St. Louis, Mo).* You should be commended on your low rate of graft revision despite imaging. In St Louis, we do not have our hybrid operating room ready yet, so the only thing I can really use for off-pump CABG is the flow probe. It looked like part of your imaging was flow probe assessment. Do you have any data to correlate your imaging with flow probe information? In other words, would flow probe data alone have prompted you to revise your grafts without the angiography data?

Dr Singh. That is an excellent question. We used both techniques in collaboration, because the evidence from our institution has shown that the flow probe is more sensitive to complete occlusions and the ICG technique was more sensitive to nonocclusive disease.

When we looked at the grafts that were not revised, at 1-year follow-up angiography, we looked at the mean pulsatility indexes, the mean diastolic flow fractions, and the mean flows. Actually, there was no difference in those that ultimately were occluded and those that were not. However, most grafts that were revised had more findings on the TTF than on the ICG. Thus there was more of a predilection for revision with positive TTF findings.

Dr Beat H. Walpoth *(Geneva, Switzerland).* We pioneered the TTF measurements 15 years ago. I think it is a nice study, but I am not sure whether you can predict the flow at a 1-year follow-up based on the initial flow. It would be marvelous, but it is so complex; there are so many factors. However, on the other hand, you had several revisions during surgery owing to bad flow or bad visualization of the graft. Therefore, I think you cannot support your conclusion, because your conclusion says that you should measure flow only in high-risk patients and sporadically. The point is, actually, that you should measure all grafts. This takes 1 minute per graft, and if you measure all grafts you will not miss patients in whom you should do a revision on site. That is how you will improve your patency in the long run. Could you comment on these aspects?

Dr Singh. What we have gleaned from our study is that there is a need for improving quality assurance and that intraoperative tools can identify potential errors and poorly constructed grafts. However, we also identified that perhaps there is still a role for clinical judgment by surgeons as to what grafts are critical and at high risk for failure, requiring revision, or what grafts should not be revised if the outcome would be poorer patency owing to technical challenge, but may not dramatically influence outcomes. As such, the collaboration of clinical judgment with objective evidence from intraoperative tools probably is what best leads to improving patency

and avoiding inappropriate graft revisions. As we have seen, although it is hard to make a meaningful conclusion from a smaller number, some of the grafts that met revision criteria, but were not revised because of attending surgeon judgment, were still patent at 1-year follow-up angiography. I think we should not go full force to say we should use it routinely; however, targeted use of clinical judgment would probably be most ideal.

Dr Walpoth. One follow-up question: If you had only one technique, which one would you prefer?

Dr Singh. Evidence from our institution, comparing ICG to TTF to the gold standard, x-ray angiography, has shown that the sensitivity and specificity of ICG for 50% to 90% stenoses and 100% stenoses is superior to that of TTF. TTF has a sensitivity and specificity for nonocclusive disease much poorer than that of ICG. Thus ICG might provide more data. Besides that, it is much more user friendly and better provides an image that attending surgeons can easily interpret as opposed to just interpreting numbers that are provided by TTF.

Dr Keith Horvath *(Bethesda, Md).* This was an excellent presentation of a difficult study to conduct. Some might assume a conclusion from this trial is that hybrid operating rooms are not really needed, because you have done a nice job showing that imaging really did not have a significant impact at the time of surgery. I am wondering whether that is a fair conclusion. My second question is this: You have demonstrated that there are many factors responsible for graft failure and that the technical aspects at the time of the grafting, although they play a role, are probably not as high of a factor in causing graft failure as we think. From what you have been able to see in the grafts that failed, was there any either qualitative or semiquantitative assessment of the distal vessel that may have been the reason for those failures? Did you learn anything in that regard? The extent of target vessel disease is probably still a much more important factor in graft failure than the technical aspects of the operation.

Dr Singh. Thank you for those two questions. Your first question concerned the role of imaging and queried the involvement of evolution of hybrid operating rooms. I think there still is a role for imaging, especially in the evolution of hybrid operating suites, because in many situations what is being done is minimal access, lower exposure, beating heart procedures. As such, these are the patients that are probably at high risk for poorer construction of distal anastomoses and, as such, intraoperative angiography or imaging should have a role.

With respect to your second question, we did note that the graft revision rate was quite low and that the occlusions at 1 year obviously are multifactorial. Many things contribute to this, including distal target characteristics. We have not looked at it in the present study, but we will be looking at the data and comparing them. One would anticipate that the degree of distal disease and the native vessel characteristics, as has been shown in the literature, would play a role in 1-year patency; however, given the randomization of the study, we believe the impact should have been balanced.

APPENDIX E1. Intraoperative and follow-up angiographic details of grafts revised or meeting revision criteria

Grafts meeting revision criteria or revised (n = 14)	Group	ICG angiography			TTF						Postop graft status
		>50% stenosis	TIMI flow	ICG result	Mean flow (mL/min)	Diastolic flow fraction (%)	Pulsatility index	TTF result	Revised?	If no, why?	
LITA-LAD	Imaging	No	III	Normal	6.0	63	7.7	Abnormal	No	Poor distal target, not reparable; small graft	Patent
SVG-D1	Imaging	No	III	Normal	8.0	41	6.7	Abnormal	No	Poor distal target, not reparable	Patent
SVG-PIV	Imaging	No	III	Normal	43.0	32	9.4	Abnormal	No	Proximal clearly visualized	Patent, with mild stenosis
SVG-OM	Imaging	No	III	Normal	18.0	20	5.9	Abnormal	No	Poor distal target, not reparable	Occluded
SVG-IM	Imaging	No	III	Normal	8.0	65	7.0	Abnormal	No	Poor distal target, not reparable	No follow-up angiography
RA-PIV	Imaging	No	III	Normal	8.0	6	18.8	Abnormal	Yes		Patent
SVG-OM1	Imaging	No	III	Normal	9.5	30	16.4	Abnormal	Yes		Occluded
SVG-PL	Imaging	No	III	Normal	16.0	53	5.5	Abnormal	Yes		No follow-up angiography
SVG-OM1	Imaging	No	III	Normal	25	85	3	Normal	Yes		Patent
LITA-OM1	Control	No	III	Normal	24	68	2	Normal	Yes		Occluded
LITA-LAD	Control	NA	NA	NA	NA	NA	NA	NA	Yes		Patent
SVG-PIV	Control	NA	NA	NA	NA	NA	NA	NA	Yes		Patent
LITA-LAD	Control	NA	NA	NA	NA	NA	NA	NA	Yes		Occluded
LITA-LAD	Control	NA	NA	NA	NA	NA	NA	NA	Yes		No follow-up angiography

ICG, indocyanine green; *TTF,* transit-time flowmetry; *TIMI,* Thrombolysis in Myocardial Infarction; *LITA,* left internal thoracic artery, *LAD,* left anterior descending artery; *SVG,* saphenous vein graft; *D,* diagonal; *PIV,* = posterior interventricular; *OM,* obtuse marginal; *IM,* intermediate; *RA,* radial artery; *PL,* posterolateral; *NA,* not applicable.